minutes and the resin-bound peptide (25 µmoles) was added to the dye. The reaction was carried out at ambient temperature for 3 hours. The mixture was filtered and the solid residue was washed with DMF, acetonitrile and THF. After drying the green residue, the peptide was cleaved from the resin and the side chain protecting groups were removed with a mixture of trifluoroacetic acid:water:thioanisole:phenol (85:5:5:5$^{v/v}$) The resin was filtered and cold t-butyl methyl ether (MTBE) was used to precipitate the dye-peptide conjugate. The conjugate was dissolved in acetonitrile:water (2:3$^{v/v}$) and lyophilized. The product was purified by HPLC to give octreotate-1,1,2-trimethyl-[1H]-benz[e]indole propanoic acid conjugate (10%,), monooctreotate-bispentylcarboxymethylindocyanine dye (Cytate 3, 60%, n = 4, R_2 = OH) and bisoctreotate-bispentylcarboxymethylindocyanine dye (Cytate 4, 30%, n = 4, R_1 = R_2).

Example 6

Synthesis of Peptide-Dye-Phototherapy Conjugates (Figure 1B , n = 4, R_1 = Octreotate, R_2 = HPPH) by Solid Phase

Bispentylcarboxymethylindocyanine dye (cyhex, 60 mg, 75 µmoles) in dichloromethane is reacted with cyanuric acid fluoride (21 mg, 150 mmoles) in the presence of pyridine (12 mg, 150 mmoles) for 30 minutes to produce an acid anhydride. One molar equivalent of 2-[1-hexyloxyethyl]-2-devinylpyropheophorbide-a (HPPH, Figure 1D, T = -$NHC_2H_4NH_2$) is added to the anhydride to form the cyhex-HPPH conjugate with a free carboxylic acid group. This intermediate is added to an activation reagent consisting of a 0.2 M solution of HBTU/HOBt in DMSO (400 µl), and a 0.2 M solution of diisopropylethylamine in DMSO (400 µl). Activation of the carboxylic acid is complete in about 30 minutes. Resin-bound peptide (octreotate, 25 µmoles), is

prepared as described in Example 4, is added to the mixture. The reaction is carried out at ambient temperature for 8 hours. The mixture is filtered at the solid residue is washed with DMF, acetonitrile and THF. After drying the dark residue at ambient temperature, the peptide derivative is cleaved from the resin and the side chain protecting groups are removed with a mixture of trifluoroacetic acid:water:thioanisole:phenol (85:5:5:5$^{v/v}$). After filtering the resin, cold t-butyl methyl ether (MTBE) is used to precipitate the dye-peptide conjugate, which is then lyophilized in acetonitrile:water (2:3$^{v/v}$).

Example 7

Synthesis of Peptide-Dye-Phototherapy Conjugates (Figure 1B , n = 4, R_1 = Octreotide, R_2 = HPPH) by Solution Phase

Derivatized HPPH ethylenediamine (Figure 1D, T = -$NHC_2H_4NH_2$; 1.1 molar equivalents) and lysine(trityl)[4] octreotide (1.2 molar equivalents) were added to a solution of bis(pentafluorophenyl) ester of cyhex (1 molar equivalent) in DMF. After stirring the mixture for 8 hours at ambient temperature, cold *t*-butyl methyl ether was added to precipitate the peptide conjugate. The crude product was purified by high performance liquid chromatography (HPLC).

Example 8

Synthesis of Peptide-Dye-Phototherapy Conjugates (Figure 1C, n = 4, R_1 = K^0-Octreotate, R_2 = HPPH, R_3 = OH) by Solid Phase

Orthogonally protected Fmoc-lysine(Mtt)^0 Octreotate was prepared on a solid support, as described in Examples 3 and 4. The Fmoc group of Fmoc-lysine(Mtt)^0 is removed from the solid support with 20% piperidine in DMF. HPPH (Figure 1D, T = -OH), pre-activated with HBTU coupled to the free a-amino group of lysine.

Example 9

Imaging of Tumor Cell Lines With Indocyanine Green

A non-invasive *in vivo* fluorescence imaging apparatus was employed to assess the efficacy of indocyanine green (ICG) in three different rat tumor cell lines of the inventive contrast agents developed for tumor detection in animal models. A LaserMax Inc. laser diode of nominal wavelength 780 nm and nominal power of 40 mW was used. The detector was a Princeton Instruments model RTE/CCD-1317-K/2 CCD camera with a Rodenstock 10 mm F2 lens (stock #542.032.002.20) attached. An 830 nm interference lens (CVI Laser Corp., part # F10-830-4-2) was mounted in front of the CCD input lens, such that only emitted fluorescent light from the contrast agent was imaged.

Three tumor cell lines, DSL 6/A (pancreatic), Dunning R3327-H (prostate), and CA20948 (pancreatic), which are rich in somatostatin (SST-2) receptors were induced into male Lewis rats by solid implant technique in the left flank area (Achilefu et al., *Invest. Radiology*, 2000, pp. 479-485). Palpable masses were detected nine days post implant.

The animals were anesthetized with xylazine:ketamine:acepromazine (1.5:1.5:0.5$^{w/v}$) at 0.8 ml/kg via intramuscular injection. The left flank was shaved to expose the tumor and surrounding surface area. A 21-gauge butterfly needle equipped with a stopcock connected to two syringes containing heparinized saline was placed into the tail vein of the rat. Patency of the vein was checked prior to administration of ICG. Each animal was administered a 0.5 ml dose of a 0.42 mg/ml solution of ICG in saline.